Statistical Analysis Plan

Sponsor:	Bristol-Myers Squibb
Protocol No./ Version	IM025006/Amendment 6 v7.0
[redacted]	
Title:	A Randomized, Double-Blind, Placebo-Controlled, 2-Part, Parallel Group, Multiple Dose Phase 2 Study to Evaluate the Efficacy and Safety of BMS-986263 in Adults with Advanced Hepatic Fibrosis from Hepatitis C who have Achieved Sustained Viral Remission
[redacted]	
SAP Version No./Date:	V1.1/19-Feb-2019

Approvals

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[redacted]

2.0 **Study Objectives**

2.1 Primary Study Objectives

- Part 1: To assess the effect of treatment with 90 mg once every week (QW) of BMS-986263 on the proportion participants with ≥ 1 stage improvement in liver fibrosis (METAVIR score), as compared to placebo after 12 weeks of treatment.

2.2 Secondary Study Objectives

Part 1:

- To assess the effect of treatment with 90 mg QW BMS-986263 on the change in collagen proportionate area (CPA), as compared to placebo after 12 weeks of treatment
- To assess the effect of treatment with 90 mg QW BMS-986263 on the proportion of participants with ≥ 1 stage improvement in liver fibrosis (Ishak score), as compared to placebo after 12 weeks of treatment
- To assess the effect of treatment with 90 mg QW BMS-986263 on the proportion of participants with ≥ 2 stage improvement in liver fibrosis (METAVIR score), as compared to placebo after 12 weeks of treatment
- To assess the effect of treatment with 90 mg QW BMS-986263 on the proportion of participants with ≥ 2 stage improvement in liver fibrosis (Ishak score), as compared to placebo after 12 weeks of treatment

- To assess the effect of treatment with 90 mg QW BMS-986263 on the proportion of participants with a ≥ 15% reduction in liver stiffness as measured by magnetic resonance elastography (MRE) compared to placebo at Week 12
- To assess the effect of treatment with 90 mg QW BMS-986263 on the change in liver stiffness from baseline as measured by MRE compared to placebo at Week 12
- To assess the safety and tolerability of 45 mg QW and 90 mg QW BMS-986263 throughout 36 weeks of treatment and follow-up
- To assess the pharmacokinetics (PK) of 45 mg QW and 90 mg QW BMS-986263
- To describe the effect of treatment with 45 mg QW BMS-986263 on liver fibrosis after 12 weeks of treatment

[redacted]

3.0 **Study Design**

3.1 Overall Study Design

This is a randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of BMS-986263 in adults with advanced hepatic fibrosis due to HCV who have achieved sustained virologic response (SVR) for at least 1 year. This study will enroll approximately 60 participants in Part 1, randomized in a 1:2:1 ratio to receive 45 mg BMS-986263 QW, 90 mg BMS-986263 QW, or placebo QW for 12 weeks. The primary study endpoint is the proportion of participants who achieve ≥ 1 stage improvement in liver fibrosis (METAVIR score) on biopsy after 12 weeks of treatment in Part 1.

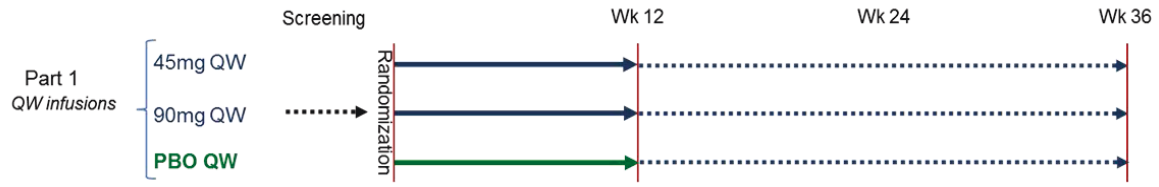
Part 1: The primary objective of Part 1 is to assess the effect of treatment with 90 mg QW BMS-986263 on the proportion participants with ≥ 1 stage improvement in liver fibrosis (METAVIR score) on biopsy, as compared to placebo after 12 weeks of treatment. This part of the study includes:

- A screening period
- A 12-week, double-blind treatment period, during which participants will receive 1 of the 3 following treatments: 45 mg BMS-986263 QW, 90 mg BMS-986263 QW, or placebo QW
- A 24-week follow-up period

[redacted]

A schematic of the study design is provided in Figure 1.

Figure 1 Study Design Schematic



PBO = placebo; QW = once weekly; Wk = Week

3.2 Sample Size Considerations

This study will enroll approximately 60 participants in Part 1, randomized via IRT (interactive response technology) in a 1:2:1 ratio to receive 45 mg BMS-986263 QW, 90 mg BMS-986263 QW, and placebo QW. The sample size for Part 1 is not based on formal statistical justification. Part 1 of the study is designed for estimation purposes; no statistical testing will be performed. A 95% confidence interval (CI) for the primary endpoint of proportion of participants with ≥ 1 stage improvement in fibrosis on biopsy after 12 weeks of treatment and odds-ratios between treatment groups will be utilized for this purpose.

3.3 Randomization

Approximately 60 participants meeting eligibility criteria during the screening period for Part 1 will be randomized into the Part 1 treatment period. These participants will be randomized via IRT in a 1:2:1 ratio to 45 mg BMS-986263 QW, 90 mg BMS-986263 QW, or placebo QW in a double-blind manner. The randomization of participants will be stratified by fibrosis stage as assessed by local pathologist (METAVIR Stage 3 or Stage 4).

4.0 **Study Variables and Covariates**

4.1 Primary Efficacy Variable

The primary efficacy variable is the METAVIR fibrosis score, which will be determined by a central pathologist using liver biopsies.

The METAVIR system is used to assess the extent of inflammation and fibrosis by histopathological evaluation in a liver biopsy of patients with HCV. It assesses liver biopsies for activity grade (A0-A3: A0 = no activity, A1 = mild activity, A2 = moderate activity, A3 = severe activity) and fibrosis stage (Stage 1 – 4: 1 = portal fibrosis without septa; 2 = portal fibrosis with few septa; 3 = numerous septa without cirrhosis; or 4 = cirrhosis).

The METAVIR fibrosis score will also be used as a secondary efficacy variable for some endpoints.

4.2 Secondary Efficacy Variables

4.2.1 Collagen Proportionate Area

There can be considerable intra- and inter-individual variation in the assessment of liver biopsy to determine fibrosis stage. Assessment of CPA is a method by which the amount (percentage) of collagen in stained tissue sections is analyzed using morphometric image analysis. This technique allows for a quantitative assessment of fibrosis. This morphometric assessment will be performed by a blinded central pathologist. The percentage of collagen proportionate area will be provided.

4.2.2 Ishak Liver Fibrosis Score

Ishak liver fibrosis scores will be done by the central pathologist using the liver biopsies. The Ishak system (0 through 6 scale) was developed to grade portal-based liver fibrosis associated with viral hepatitis:

- 0: No fibrosis
- 1: Fibrous expansion of some portal areas, with or without short fibrous septa
- 2: Fibrous expansion of most portal areas, with or without short fibrous septa
- 3: Fibrous expansion of most portal areas with occasional portal to portal bridging
- 4: Fibrous expansion of portal areas with marked bridging (portal to portal as well as portal to central)
- 5: Marked bridging (portal–portal and/or portal–central) with occasional nodules (incomplete cirrhosis)
- 6: Cirrhosis, probable or definite

4.2.3 Liver Stiffness by MRE

MRE is a noninvasive medical imaging technique approved by FDA in 2009. It quantitatively measures in kilopascal (kPA) the stiffness of soft tissues by introducing shear waves and imaging their propagation using magnetic resonance imaging (MRI). In this study, MRE will be used to quantitate liver stiffness as a surrogate biomarker of liver fibrosis. The central imaging facility will perform all MRE imaging analyses.

[redacted]

[redacted]

[redacted]

4.5 Safety Variables

The safety of BMS-986263 will be assessed by evaluation of the incidence of all adverse events (AEs) and serious adverse events (SAEs), [redacted] electrocardiogram (ECG) monitoring, physical examinations, vital signs, [redacted].

4.5.1 Adverse Events

The definition of adverse events and serious adverse events as well as their time periods for collection can be found in the protocol Section 8.6.2 and Protocol Appendix 2. The event (term), along with its start and stop dates, maximum intensity (mild, moderate, or severe), seriousness (yes/no), relationship to the IP (yes/no), action taken with regard to the IP, and outcome will be recorded in the electronic case report form (eCRF).

[redacted]

Additional details for infusion related reactions will be collected including clinical signs and symptoms as well as the location, characteristics and severity of those signs or symptoms, and start and end time of the reaction.

4.5.2 Laboratory Data

Hematology, serum chemistry, urinalysis, and other assessments are listed below. A central laboratory will perform the analyses and will provide reference ranges for these tests.

Hematology		
• CBC • PT • PTT • INR	• WBC (absolute) • Hemoglobin • Hematocrit • MCV	• MCH concentration • Red cell distribution width • Platelet count
Blood Chemistry		
• AST • ALT • Total bilirubin • Direct bilirubin • ALP • LDH • GGT • Creatinine	• Creatinine clearance • Creatine kinase • BUN • Uric acid • Glucose • PTH • Total protein • Albumin sodium	• Potassium • Chloride • Carbon dioxide • Calcium • Phosphorus • Glomerular filtration rate
Urinalysis		
• pH • Specific gravity • Protein	• Glucose • Ketones • Leukocyte esterase	• Nitrite • Creatinine • Microscopic examination (only to follow-up abnormal findings)
[redacted]		
HbA1C		
[redacted]		
Serology/viral load	• HCV viral load (RNA) • HBsAg	• HbcAb and HBV viral DNA if HbcAb-positive.
[redacted]		

[redacted]

Other Analyses		
[redacted]	• FSH • AFP [redacted]	• Illegal drugs of abuse (urine or serum; amphetamine, barbiturate, benzodiazepines, marijuana, cocaine, opiate, or PCP) • pregnancy test (WOCBP only).

AFP = alpha-fetoprotein; ALP = alkaline phosphatase; [redacted] ALT = alanine aminotransferase, AST = aspartate aminotransferase; [redacted] BUN = blood urea nitrogen; [redacted] CBC = complete blood count; [redacted] CVD = cardiovascular disease; DNA = deoxyribonucleic acid; [redacted] GGT = gamma-glutamyl transferase; [redacted] FSH = follicle stimulating hormone; HbA1c = hemoglobin A1c; HBsAg = hepatitis B surface antigen; HbcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; [redacted] INR = international normalized ratio; LDH = lactate dehydrogenase; [redacted] MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; MOA = mechanism of action; [redacted] PCP = phencyclidine; PT = prothrombin time; PTH = parathyroid hormone; PTT = partial thromboplastin time; [redacted] WBC = white blood cell; WOCBP = women of childbearing potential [redacted]

4.5.3 Electrocardiograms

Variables collected from a central vendor for electrocardiograms include mean heart rate, RR interval, PR interval, QRS duration, QT interval, QTcB interval, QTcF interval, interpretation, atrioventricular conduction, axis and voltage, chamber hypertrophy or enlargement, intraventricular-intra atrial conduction, myocardial infarction (if applicable), pacemaker status, sinus node rhythms and arrhythmias (if applicable), supraventricular arrhythmias and tachyarrhythmias, ST segment, T and U waves, technical quality, and ventricular arrhythmias and tachyarrhythmias.

4.5.4 Physical Examinations

A full examination will include general appearance, skin, head, eyes, ears, nose, throat, neck, thyroid, chest/lungs, heart, abdomen, lymph nodes, extremities, height, and body weight. Abbreviated physical examinations will be performed at the other time points, which will include an abdominal exam, assessments for ascites and hepatic encephalopathy, as well as symptom-focused assessments. An abbreviated examination may note any changes in the participant's condition (body systems) since the last assessment and does not preclude examination of any of the other body systems as clinically indicated. Physical exam variables include exam date and time [redacted] body system, result, whether abnormal and if abnormal the result, and whether this is clinically significant.

4.5.5 Vital Signs

Vital signs variables include height, weight, body mass index (BMI), temperature, systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and clinical significance.

4.5.6 Bone Density Testing

DXA will be performed to assess bone density. The clinical sites will be trained in imaging procedures prior to scanning the first study participant. The baseline Z-score to determine participant's eligibility will be based on local radiologist read at the clinical site. [redacted] Variables include the date and time of assessment, and total BMD and T- and Z-scores for hip, lumbar spine, and femoral neck. In addition, the number of lumbar spine segments and the segments included in the assessment (L1, L2, L3, L4) will be collected.

4.6 Other Variables

Other variables that will be collected include participant demographics (birth date, age, sex, ethnicity, race), general medical history, prior and concomitant medications, hospitalizations, and diagnostic and/or medical procedures that occur.

In addition, variables will be collected for informed consent and re-consent if applicable, eligibility including pregnancy testing and childbearing potential, randomization or reason for non-randomization, ultrasound for detection of hepatocellular carcinoma (HCC) at screening, and previous enrollment and dates enrolled in a previous BMS study. Details of the regimen used to treat and cure Hepatitis C (date of sustained virologic response, treatment, start and end date, dose and unit per administration, frequency, and route) as well as disease diagnosis and specific disease history (date of diagnosis, and history of impaired fasting glucose and diabetes) will also be recorded.

Treatment exposure variables will include start and end dates and times, total volume prepared (mL), actual volume and whether different from total volume prepared and reason (Adverse Event or Other), infusion rate (mL/hour), whether administration was interrupted and reason (Adverse Event or Other), and whether administration was resumed. Pre-treatment antihistamine and corticosteroid variables will include the medication name, date and start and end times, dose and unit, and route.

End of treatment and end of study dates and reasons will be collected. When applicable, date of death, primary cause of death, and whether autopsy was performed will be recorded.

4.7 Pharmacokinetics [redacted] Variables

Blood for PK samples will be drawn at several time points according to the sampling schedules shown in the protocol Section 8.6.3. Samples from participants randomized to placebo will not be analyzed. Plasma concentrations of BMS-986-263, [redacted] will be measured.

[redacted]

[redacted]

4.9 Predetermined Covariates and Prognostic Factors

Subgroup analyses will be presented by baseline METAVIR fibrosis stage determined by central pathologist where specified in the TFL shells. Other subgroups may include Pro-C3 level (split at the median). Summary tables and/or figures may be provided for these analyses.

5.0 **Definitions**

5.1 Screen Failures, Retesting, and Rescreening

Screen failures are defined as participants who consent to participate in the clinical study (i.e., enroll) but are not subsequently randomized into the study.

Rescreening is allowed but the participant must wait at least four weeks after the date of screen failure to attempt to re-enroll. The protocol delineates which screening procedures need repeating and under what circumstances.

5.2 Baseline

Baseline is defined as the last measurement prior to first dose of double-blind study treatment (BMS-986263 or matching Placebo). Admissible prior biopsies and biopsies performed during screening will be used to determine eligibility (i.e., liver fibrosis stage), and tissue from these biopsies will be used as the baseline sample for the primary endpoint analysis. The requirement that prior biopsies occur within 8 weeks prior to screening ensures that the acquired biopsy sample accurately reflects the condition of the participant at baseline to enable a valid analysis.

Many pre-infusion measures are collected per-protocol on study day 1 (randomization). For variables specified in the schedule of events to be collected prior to infusion the analysis will assume they were collected per-protocol and as such they will qualify as baseline measures.

5.3 Actual Treatment

All analyses conducted on the Safety Analysis Set will be performed using the Actual Treatment. Actual treatment is defined as the highest dose and frequency of active study treatment (BMS-986263) that a participant receives at any time during their participation in the study. Participants who only receive Placebo will be analyzed as such.

5.4 Change and Percentage from Baseline

Change from baseline (CFB) will be calculated as (post-baseline value – baseline value). CFB will be calculated for participants with both a baseline and post-baseline value as applicable. Percent CFB will be calculated as (CFB/baseline)*100, where applicable. If a baseline value has not been recorded for a parameter, then CFB will not be calculated for that parameter. Participants with missing CFB values will be excluded from analyses in which CFB is the endpoint. In cases where baseline is zero and the post-baseline value is also zero percent CFB will be considered zero percent.

5.5 Adverse Event, Serious Adverse Event

The definitions of AE and SAE can be found in the Protocol Appendix 2. If an adverse event causality or severity is missing, the causality or severity will not be imputed.

The following imputation rules will be used for AE:

Imputation Rules for Partial Dates (D = day, M = month, Y = year)

Parameter	Missing	Additional Conditions	Imputation
Start date for AEs	D	M and Y same as M and Y of first dose of study treatment	Date of first dose of study treatment
		M and/or Y not same as date of first dose of study treatment drug	First day of month
	D and M	Y same as Y of first dose of study treatment	Date of first dose of study treatment
		Y prior to Y of first dose of study treatment but same as Y of screening date	Date of screening date
	D, M, Y	None – date completely missing	Date of first dose of study treatment
Stop date for AEs	D	M and Y same as M and Y of the Follow-up visit	Date of the Follow-up visit
		M and/or Y not same as date of the Follow-up visit	Use last day of month
	D and M	Y same as Y of the Follow-up visit	Date of the Follow-up visit
		Y not same as Y of the Follow-up visit	Use Dec 31
	D, M, Y	None – date completely missing	No imputation, but assume ongoing

Note: In all cases, if an estimated start date is after a complete stop date, use the first day of the stop date month. Similarly, if the estimated stop date is before a complete or imputed start date, use the last day of the start date month.

For example for AE start date imputation, if a participant is dosed on 15MAY2018 and has an AE start date reported as MAY2018 the imputation would be 15MAY2018, but if the AE start date was reported as JUN2018 the imputation would be 01JUN2018.

For example for AE stop date imputation, if a participant follow-up visit or cutoff date is 15MAY2018 and has an AE stop date reported as MAY2018 the imputation would be 15MAY2018, but if the AE stop date was reported as MAR2018 the imputation would be 31MAR2018.

5.6 Treatment-Emergent Adverse Event (TEAE)

Treatment-emergent adverse events (TEAEs) are those which first occur or increase in severity or relationship to study treatment after the first dose of study treatment and not more than 30 days after the last dose of study treatment. All Adverse Events (AEs) which change in severity or relationship to study treatment are assigned a new start date and captured as a new record.

[redacted]

5.8 Study Treatment

For the purposes of the calculations included in this SAP, study treatment will include only doses of BMS-986263 or placebo.

5.9 Treatment Duration (weeks)

Treatment duration (weeks) will be calculated as:

Part 1: (date of last dose of study treatment* during Part 1 – date of first dose of study treatment during Part 1 + 7)/7. The additional 7 days are added to account for the last week of treatment.

*for the purposes of these calculations, study treatment refers to BMS-986263 or placebo.

5.10 Study Day

Study day is defined relative to the date of the first dose of study treatment. For assessments that occur on or after this visit date, study day is calculated as (assessment date – first dose date + 1). For assessments that occur prior to first dose date, study day will be calculated as (assessment date – first dose date); there is no Study Day 0. Study Day 1 is the day of first study treatment received.

5.11 Prior and Concomitant Medications

All medications taken from within 4 weeks before the first dose of study treatment until last visit must be recorded on the eCRF. Prior medications are defined as medications taken within 4 weeks of the first dose of study treatment and discontinued before the first dose of study treatment. Concomitant medications are defined as any medication taken after the first dose of study treatment until last visit

Imputation Rules for Partial Dates (D = day, M = month, Y = year)			
Parameter	**Missing**	**Additional Conditions**	**Imputation**
Start date	D only	M and Y same as M and Y of first dose of study treatment	Date of first dose of study treatment

Imputation Rules for Partial Dates (D = day, M = month, Y = year)			
Parameter	**Missing**	**Additional Conditions**	**Imputation**
		M and/or Y not same as date of first dose of study treatment	First day of month
	M and D	Y same as Y of first dose of study treatment	Date of first dose of study treatment
		Y not same as Y of first dose of study treatment	Use Jan 01 of Y
	M, D, and Y	None – date completely missing	Day prior to date of first dose of study treatment
Stop date	D only	M and Y same as M and Y of the Follow-up visit	Date of the Follow-up visit
		M and/or Y not same as date of the Follow-up visit	Last day of month
	M and D	Y same as Y of the Follow-up visit	Date of the Follow-up visit
		Y not same as Y of the Follow-up visit	Use Dec 31 of Y
	M, D, and Y	None – date completely missing and NOT ongoing	Date of the Follow-up visit

Note: In all cases, if an estimated start date is after a complete stop date, use the first day of the stop date month. Similarly, if the estimated stop date is before a complete or imputed start date, use the last day of the start day month.

For example for a concomitant medication start date imputation, if a participant is dosed on 15MAY2018 and has a concomitant medication start date reported as MAY2018 the imputation would be 15MAY2018, but if the concomitant medication start date was reported as JUN2018 the imputation would be 01JUN2018.

For example for a concomitant medication stop date imputation, if a participant follow-up visit or cutoff date is 15MAY2018 and has a concomitant medication stop date reported as MAY2018 the imputation would be 15MAY2018, but if the concomitant medication stop date was reported as MAR2018 the imputation would be 31MAR2018.

Note, if a medication is missing an end date and is recorded as ongoing, it will be classified as concomitant. Partial dates should be imputed before the classification of prior or concomitant.

[redacted]

[redacted]

5.14 Other Calculations

[redacted]

Method of BMI Calculation:

- Use actual height and weight collected on the same day. Whenever possible, body weight should be measured using the same scale throughout the study.
- To calculate BMI:
  - Convert weight pounds to kg (kg = pounds / 2.2)
  - Convert height inches to centimeters (cm = inches × 2.54)
  - BMI = (weight in kg) / (height in cm/100)^2
  - Round to 1 decimal place (if 0.05 or greater, round up)

6.0 **Analysis Sets**

The following analysis sets are defined for analysis purposes:

Analysis Set	**Description**
Enrolled[a]	All participants who sign informed consent
Randomized	All participants who are randomized to a treatment, analyzed as per randomized treatment.
Modified intent-to-treat (mITT)	All participants who are randomized to a treatment and receive at least 1 dose of study treatment analyzed as per randomized treatment. All primary efficacy analyses will be conducted using this analysis set.

[redacted]

Pharmacokinetic	All participants who receive at least 1 dose of BMS-986263 and have any available concentration-time data
Safety (As-treated)	All randomized participants who receive at least 1 dose of study treatment, analyzed according to the treatment actually received. The treatment may differ from that to which the participant was originally randomized. All safety analyses will be conducted using this analysis set.

[a] For the Enrolled Analysis Set, there may be some cases where data is analyzed by treatment group. If this is the case, any participants who are in the Enrolled Analysis Set but were not randomized (i.e. not in the Randomized Analysis Set), those participants will not be included in any particular treatment group, but will be included in any overall summary.

[redacted]

8.0 **Data Review**

8.1 Data Handling and Transfer

Data will be entered and exported as SAS® version 9.4 or higher datasets. Converted datasets will be created using SAS and following standard Clinical Data Interchange Standards Consortium Standard Data Tabulation Model conventions. Analysis datasets will be created using SAS and following CDISC Analysis Data Model standards.

Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 20.1 or later at the time of the analysis to assign a system organ class (SOC) and preferred term (PT) to each event. Prior and concomitant medications and steroids will be coded using the World Health Organization Drug Dictionary WHO DD 2017 SEP01 DDE+HD or later at the time of the analysis using anatomical therapeutic classification (ATC) and PT.

Additional details can be found in the PRA Data Management Plan, Data Transfer Plans, and the Data Quality Plan for this study. Data will be cleaned to prespecified levels for all data base locks or freezes, including for the interim and final analysis.

8.2 Data Screening

Beyond the data screening built into the PRA Data Management Plan, the PRA programming of analysis datasets and TFLs provides additional data screening. Presumed data issues will be output into SAS logs identified by the word “Problem” and extracted from the logs by a SAS macro and sent to Data Management.

Designated staff of BMS may be unblinded (obtaining the randomization codes) prior to database lock to facilitate the bioanalytical analysis of PK samples and immunogenicity.

9.0 **Statistical Methods**

All analyses will use SAS® version 9.4 or higher

- Descriptive summaries will be tabulated by part, treatment group, and in total within part unless otherwise specified.
- Categorical data will be presented using counts and percentages, with the number of participants in each category as the denominator for percentages
    - For by-visit summaries denominators will be adjusted to reflect the number of participants in the study at the time of the visit
    - Percentages will be rounded to one decimal place except 0% and 100% which will be displayed without any decimal places and percentages will not be displayed for zero counts.
- Continuous data will be summarized using the number of observations (n), mean, standard deviation (SD), median, first quartile, third quartile, minimum, and maximum unless otherwise specified. Minimum and maximum will be rounded to the precision of the original value.
    - Mean,median, first and third quartiles will be rounded to 1 decimal place greater than the precision of the original value. The SD will be rounded to 2 decimal places greater than the precision of the original value, with the original value having up to a maximum of 3 decimal places.
- P-values will be presented to 3 decimal places where presented in the TFL shells
- Separate tables, figures, and listings will be presented for Part 1 and Part 2 of the study. Data will not be pooled across Parts 1 and 2.

9.1 Participant Disposition

The number and percentage of participants in each analysis set will be presented. The number and percentage of participants randomized but not treated will be included.

The number of participants enrolled/randomized will be presented by study part, total within part and by treatment group, along with the number and percentage of participants who completed, discontinued, and are ongoing at the time of the data cut in total within part and by treatment group. The number and percentage of participants who completed the treatment period, withdrew from study treatment prematurely and a breakdown of the corresponding reasons for withdrawal from study treatment will be presented. The number and percentage of participants who completed the study, were ongoing at the time of the data snapshot (for the interim analysis report only), withdrew from the study prematurely, and a breakdown of the corresponding reasons for withdrawal will be presented. The summary will be presented by study part, treatment group, and total within part for the Randomized (RAS) Analysis Set. Also, by-participant listings will be generated.

9.2 Demographic and Baseline Characteristics

The following baseline demographic characteristics will be summarized by study part, treatment group and in total within part based on the RAS: sex, race, ethnicity, age, age group (<65 years, 65-<75 years, and >=75 years, as well as Adults [18-64 years], From 65-84 years, and 85 years and over), weight, height, body mass index (BMI).

The following baseline disease characteristics will be summarized by part, treatment group and in total within part based on the RAS: METAVIR liver fibrosis stage used for randomization as well as via central reader, history of impaired fasting glucose or diabetes, months from Hepatitis C sustained virologic response to randomization, [redacted] baseline AST, ALT and INR, baseline MRE,FibroScan, and CPA values, and baseline Pro-C3.

General medical history will be summarized for the Safety Analysis Set by part, treatment group, and in total within part. The number and percentage of participants with each event will be presented by SOC and PT. Note that counting will be by participant not event and participants are only counted once within each SOC and PT.

Prior medications summaries will be presented for the Safety Analysis Set by part, treatment group, and in total within part. The number and percentage of participants with each prior medication will be presented by ATC and PT. Note that counting will be by participant and participants are only counted once within each ATC and PT.

9.3 Important Protocol Deviations

Important protocol deviations will be summarized by number and percentage of participants experiencing each deviation category. All protocol deviations will be listed.

9.4 Prior and Concomitant Medications

Based on the Safety Analysis Set, prior and concomitant medications will be summarized by part, treatment group, and in total within part. The number and percentage of participants using each medication will be displayed together with the number and percentage of participants using at least one medication for each ATC and PT. A by-participant listing will also be presented.

9.5 Efficacy Analyses

All efficacy analyses, both primary and secondary, will be performed on the Modified-Intent-to-Treat (mITT) analysis set.

9.5.1 Primary Efficacy Analysis

The primary efficacy endpoint is the proportion of participants who achieve ≥ 1 stage improvement in fibrosis (METAVIR score) on biopsy after 12 weeks of treatment in Part 1. A “response” indicates the participant

did achieve a ≥ 1 stage improvement in fibrosis. Summary tables will be provided for overall response and response by baseline METAVIR fibrosis stage via central reader (Stage less than 4, Stage 4), and shift tables will also be provided. Participants without an efficacy measurement at Week 12 will be considered as "non-responders". Spaghetti plots will also be provided for each treatment group.

9.5.1.1 Part 1

To evaluate the effect of BMS-986263 (90 mg QW) on METAVIR Fibrosis Stage at Week 12, a 95% exact CI of response rate for treatment versus placebo will be used to estimate the difference between the proportion of participants with ≥ 1 stage improvement in fibrosis on liver biopsy. Additionally, the odds ratio of each treatment will be used to estimate improvement of treatment as compared to placebo for the proportion of participants with ≥ 1 stage improvement in fibrosis on biopsy at Week 12.

9.5.2 Secondary Efficacy Analyses

Secondary efficacy endpoints are as follows:

- Change in CPA, as compared to placebo after 12 weeks of treatment in Part 1
- Proportion of participants with ≥ 1 stage improvement in liver fibrosis (Ishak score), as compared to placebo after 12 weeks of treatment in Part 1
- Proportion of participants with ≥ 2 stage improvement in liver fibrosis (METAVIR score), as compared to placebo after 12 weeks of treatment in Part 1
- Proportion of participants with ≥ 2 stage improvement in liver fibrosis (Ishak score), as compared to placebo after 12 weeks of treatment in Part 1
- Proportion of participants with ≥ 15% decrease from baseline in liver stiffness as measured by MRE at Day 85 in Part 1
- Change from baseline in liver stiffness as measured by MRE Day 85 in Part 1

9.5.2.1 Collagen Proportionate Area

The change from baseline in collagen proportionate area will be analyzed using an Analysis of Covariance (ANCOVA) at Week 12 for Part 1. The model will include a fixed factor for treatment group and a covariate for baseline CPA. Contrasts will be used to compare the adjusted mean change from baseline between each treatment group and placebo and CIs will be presented for each comparison. In addition to actual, change from baseline, and percent change from baseline summaries by time point, box plots by treatment group and spaghetti plots by participant by treatment group will be provided.

9.5.2.2 METAVIR and Ishak Fibrosis Scores

An analysis similar to that used for the primary efficacy variable will be conducted for secondary efficacy analyses of the proportion of patients with ≥1 or ≥2 stage improvement in liver fibrosis according to Ishak and METAVIR scores.

9.5.2.3 MRE Liver Stiffness

An analysis similar to that used for the primary efficacy variable will be conducted for the proportion of participants with ≥15% decrease in MRE liver stiffness. An analysis similar to that used for the secondary endpoint of CPA will be conducted for continuous MRE liver stiffness.

[redacted]

[redacted]

9.6 Safety Analyses

9.6.1 Extent of Study Treatment Exposure

Treatment duration will be summarized based on the Safety Analysis Set by treatment group. The following summaries will be included:

- Number of participants receiving at least 1 dose
- Number of participants receiving at least 1 dose of pre-treatment antihistamine
- Number of participants receiving at least 1 dose of pre-treatment corticosteroid
- Summary of number of doses administered
- Summary of total dose administered (mg)
- Summary of participants with an interrupted infusion
- Summary of weeks of exposure

A by-participant listing will be presented. Data on pre-treatment antihistamine and/or steroids will be listed.

9.6.2 Adverse Events

All TEAE summaries will be generated based on the Safety Analysis Set by treatment group and total. A summary of TEAEs will be generated and will include the number of events reported and the number and percentage of participants reporting:

- at least one AE
- any severe AE
- any treatment-related AE
- [redacted]
- any severe treatment-related AE
- any AE with outcome of death
- any SAE
- any treatment-related SAE
- any AE leading to the discontinuation of study treatment
- any treatment-related AE leading to discontinuation of study treatment
- any AE leading to discontinuation from the study
- any treatment-related AE leading to discontinuation from the study.

A summary of AEs will be presented by MedDRA SOC and PT. A breakdown of the number and percentage of participants reporting each TEAE, categorized by SOC, PT, and maximum severity, will be presented. Note that counting will be by participant not event and participants are only counted once within each SOC or PT. An additional summary of treatment-related TEAEs by SOC, PT, and maximum severity will be presented.

Summaries of severe TEAE, treatment-related TEAE, severe treatment-related TEAE, TEAE with outcome of death, serious TEAE, treatment-related serious TEAE, TEAE leading to study treatment discontinuation, treatment-related TEAE leading to study treatment discontinuation, TEAE leading to study discontinuation, and treatment-related TEAE leading to study discontinuation will also be provided, grouped by SOC and PT.

The first row on every treatment-emergent AEs summary will be the number and percentage of participants reporting at least one TEAE. Subsequent rows will be presented in descending order of participant counts in total with the most common SOC first, followed within each SOC by the PTs in descending participant count order.

A by-participant listing of all AEs will be provided. Details such as clinical signs and symptoms will be listed for infusion related reactions.

[redacted]

9.6.4 Deaths and Serious Adverse Events

A summary of SAEs, categorized by SOC and PT and coded according to the MedDRA dictionary, will be presented by treatment group and total in the Safety Analysis Set. Note that counting will be by participant not event and participants are only counted once within each SOC or PT. All SAEs will be listed by participant. An additional summary of treatment-related SAEs will be presented by SOC and PT.

AEs with an outcome of death will be summarized by SOC and PT. All AEs with an outcome of death will be listed.

9.6.5 Laboratory Data

Based on the Safety Analysis Set, continuous laboratory results will be summarized using International System (SI) of units by visit, treatment group, and pooled BMS-986263. Categorical results such as those for urinalysis will be summarized by number and percentage of participants in each category. These summaries will be based on central laboratory results. Summaries will present both actual and change-from-baseline results for continuous values. Not all clinical lab values will be summarized. Refer to the TFL shells for the specific parameters that will be summarized. Baseline to maximum postbaseline shift tables during the treatment period will be presented for hematology, blood chemistry, metabolic panel, and Hba1c and these summaries will not be pooled by treatment group.

Elevated postbaseline values will be descriptively summarized by counts and percentages of participants ever experiencing specified elevated values per the TFL shells at any postbaseline time point for ALT, AST, Total Bilirubin, alpha-fetoprotein, [redacted].

Laboratory values below the lower limit or above the upper limit of quantification will be set equal to the lower or upper limit, respectively, for summary tables. These actual values will be displayed in the listings.

In rare circumstances where the number of evaluable lumbar spine segments changes over time for bone mineral density results, only participants with the same number and same segments as their baseline assessment will be included in change from baseline summaries of lumbar spine values. In addition, only participants with at least 2 evaluable lumbar spine segments at baseline will be included in the summary of the baseline time point. [redacted]

Where specified in the TFL shells, figures will be provided for mean change from baseline by timepoint by treatment group, with error bars for standard deviation of the mean change from baseline.

All laboratory data specified in the summary tables will be present in listings.

9.6.6 Vital Signs, ECGs, Physical Examination, and Weight

Based on the Safety Analysis Set, vital sign and 12-lead ECG parameters will be summarized by Part, visit, treatment group, and pooled BMS-986263. All vital signs and ECG results will be listed.

ECG results will be summarized for continuous variables and will be presented for the absolute result and CFB. QTc values will be presented with the implementation of corrections (i.e., Bazett's and Fridericia's) as defined in ICH Guidelines E14 by the following categories:

Absolute QTc interval prolongation:

- QTc interval > 450ms
- QTc interval > 480ms
- QTc interval > 500ms

Change from baseline in QTc interval:

- QTc interval increases from baseline >30ms
- QTc interval increases from baseline >60ms.

Total ECG impression as assessed by central reader and findings will be listed.

Physical examination results and other safety data will be listed.

9.6.7 Pharmacokinetics, [redacted]

BMS-986263, [redacted] plasma concentrations will be listed and summarized descriptively by dose, day and time among the PK Analysis Set. [redacted]

[redacted]

9.7 Methods for Handling Dropouts and Missing Data

Imputation for missing dates for AEs and concomitant medications have been addressed in previous sections (5.6 and 5.12 respectively). [redacted] Assumptions for laboratory values below or above the limits of quantification have been specified in Section 9.6.5. Participants without an efficacy measurement at Week 12 will be considered as "non-responders". No other imputations or missing data analyses are planned.

9.8 Multiplicity

There will be no adjustment for multiplicity. Many analyses will be considered descriptive in nature.

9.9 Pooling of Sites and Regional Analyses

There will be no pooling of sites in these analyses.

10.0 Validation

PRA's goal is to ensure that each Table, Figure, and Listing (TFL) delivery is submitted to the highest level of quality. The quality control procedures will be documented separately in the study specific quality control plan.

[redacted]

Appendix 1 Glossary of Abbreviations

Term	Definition
[redacted]	
AE	adverse event
[redacted]	
AFP	alpha-fetoprotein
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	Analysis of Covariance
[redacted]	
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Classification
BMD	bone mineral density
BMI	body mass index
BMS	Bristol-Myers Squibb
[redacted]	
BUN	blood urea nitrogen
[redacted]	
CDISC	Clinical Data interchange Standards Consortium
CFB	change from baseline
CI	confidence interval
[redacted]	
CMH	Cochran Mantel-Haenszel
CPA	collagen proportionate area
CRF	case report form
eCRF	electronic case report form
CSR	clinical study report
[redacted]	
DMC	Data Monitoring Committee
DMC	data monitoring committee
DXA	dual-energy X-ray absorptiometry
ECG	electrocardiogram
[redacted]	
ET	End of Treatment
FDA	U.S. Food and Drug Administration
[redacted]	
FSH	follicle stimulating hormone
GGT	gamma-glutamyl transferase
HbcAb	hepatitis B core antibody
HbsAg	hepatitis B surface antigen
HbsAb	hepatitis B surface antibody
HCC	hepatocellular carcinoma
HCV	hepatitis C virus

[redacted]	
ICF	informed consent form
ICH	International Council on Harmonization
INR	international normalized ratio
IP	investigational product
IRT	interactive response technology
LDH	lactate dehydrogenase
[redacted]	
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MRE	magnetic resonance elastography
MRI	magnetic resonance imaging
[redacted]	
OR	odds ratio
[redacted]	
PCP	phencyclidine
[redacted]	
PI	principal investigator
PK	Pharmacokinetics
[redacted]	
PT	Preferred term
PTT	partial thromboplastin time
QW	once every week
Q2W	once every 2 weeks
Q4W	once every 4 weeks
RAS	Randomized analysis set
RNA	ribonucleic acid
[redacted]	
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
SVR	sustained virologic response
TA	Therapeutic Area
TEAE	treatment-emergent adverse event
TFL	tables, figures, and listings
[redacted]	
WOCBP	women of childbearing potential

Appendix 2 Tables, Figures, Listings

Refer to the study TFL shell document.

Appendix 3 Statistical Appendices

Statistical appendices will be provided for primary endpoints containing raw SAS output. For ANCOVA analyses of secondary endpoints, appendices will be produced including plots to assess residuals and model fit.

[redacted]